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CASE REPORT

Unilateral Agenesis of the Internal Carotid Artery in CHARGE Syndrome

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CHARGE syndrome is a multisystemic disorder comprising colobomas, heart defects, choanal atresia, retarded growth and development, genital hypoplasia, ear anomalies and deafness. The *CHD7* gene on chromosome 8q12.1 was recently shown to be a major gene involved in the etiology of this syndrome. We describe a girl with CHARGE syndrome who had a novel mutation of *CHD7* associated with agenesis of the left internal carotid artery. She had presented with recurrent episodes of photophobia and vomiting since the age of 6 years. Since her symptoms were well controlled by cyproheptadine, migraine-like attacks were considered. *CHD7* molecular confirmation in this patient provides further evidence to support the occurrence of a vascular anomaly suggested from animal models of CHARGE syndrome with molecular delineation. We report this case to emphasize the importance of neurologic signs of photophobia and to highlight the broad clinical variability in this pleiotropic disorder.

1. Introduction

CHARGE syndrome is a nonrandom clustering of congenital anomalies including colobomas, heart defects, choanal atresia, retarded growth and development, genital hypoplasia, ear anomalies, and deafness.[1] Many other developmental anomalies have been reported in CHARGE syndrome,[2] and the syndrome is considered a pleiotropic disorder consisting of an association of several clinical features.[3] Approximately 60–65% of CHARGE syndrome patients[4–6] present with the *CHD7* mutation since the causative locus was determined in 2004.[7] Variable phenotypes of CHARGE syndrome with the *CHD7* mutation have been confirmed from animal models. Vascular anomalies are also expected in the phenotypes of *CHD7* mutation cases from animal models.[8] Currently, no vascular anomalies have been reported in CHARGE syndrome with the *CHD7* mutation in humans.[8] Recurrent photophobia and vomiting similar to the phenomenon of migraine-like behavior have also never been reported in CHARGE syndrome. Since the patient's symptoms were well controlled by cyproheptadine, we suggested that migraine-like attacks should be considered. We report a case with a novel *CHD7* mutation presenting with recurrent episodes of photophobia and vomiting relieved by cyproheptadine, possibly stemming from the symptoms of migraines associated with unilateral agenesis of the left internal carotid artery (ICA).

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2. Case Report

Our patient was an 8-year-old Taiwanese girl. She was born at 40 weeks of gestation with a birth weight of 2450 g and a head circumference of 45 cm to nonconsanguineous and phenotypically normal parents. There was no known family history of metabolic disease. Polyhydramnios was noted prenatally. Soon after birth, we found atrial septum defect, tracheoesophageal fistula, and esophageal atresia because of respiratory and feeding problems. She received corrective surgery on the third day. Iris coloboma and a cone shaped auricle (Figure 1) were also found. The choanae were intact. Bilateral hearing loss (>100 dB) and left facial nerve palsy were noted during the newborn period. A high-resolution computed tomography scan of temporal bones revealed bilateral cochlear hypoplasia, which was more severe on the left side. The vestibules appeared small, and semicircular canals were absent bilaterally. The absence of the left carotid canal is shown in Figure 2A. Magnetic resonance angiography of the brain revealed agenesis of the left ICA and a normal left external carotid artery (Figure 2B). The diagnosis of CHARGE was suggested because of coloboma, heart defects, and ear abnormalities. Since the age of 6 years, the patient had recurrent episodes of photophobia, vomiting, and decreased activity. Similar attacks occurred for a duration of approximately 1–2 days every 2–3 months. Simultaneous electroencephalograms revealed left central spike activity. Neither photophobia nor vomiting occurred after treatment with cyproheptadine. At 7 years old, the patient's weight was 15 kg (<3 percentile) and length was 104 cm (<3 percentile). She spoke no meaningful words. Development evaluation with Leiter-R revealed borderline development with a full IQ of 73 and a brief IQ of 76. Serum luteinizing hormone, follicle stimulating hormone, and estradiol levels were undetectable. One heterogeneous mutation of c.7226-7227 insT in exon 34 of chromodomain helicase DNA-binding protein 7 on chromosome 8q12.1 was identified (Figure 3), and CHARGE syndrome was diagnosed. An informed consent to publish clinical and molecular data as well as clinical photographs was obtained from the family.

Figure 1 Photograph of a cone-shaped auricle in the patient.

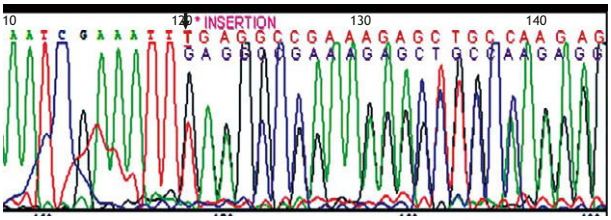

Figure 3 One heterogeneous mutation c.7226-7227 insT in exon 34 of the *CHD7* gene was found (arrow).

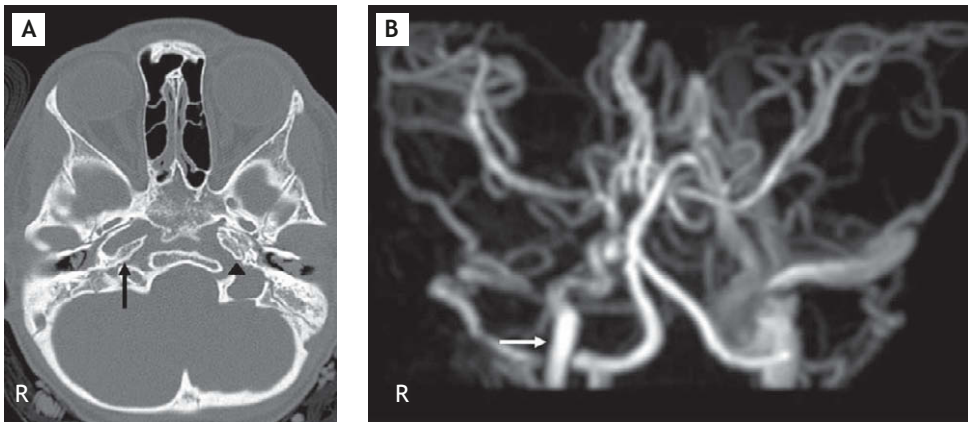

Figure 2 (A) Computed tomography of the skull base showing the absence of the carotid canal on the left (arrowhead) and a normal-sized canal on the right (arrow). (B) Magnetic resonance angiography of the brain showing agenesis of the left internal carotid artery and preservation of the right internal carotid artery (arrow). R=right side.

3. Discussion

Our case fulfilled three of the major (coloboma and characteristic ear and cranial nerve dysfunction) and five of the minor diagnostic criteria (developmental delay, congenital heart disease, dysmorphic features, growth deficiencies, and tracheoesophageal fistula) of CHARGE syndrome according to Blake et al.[9] The presentation is also consistent with typical CHARGE syndrome suggested by Verloes.[2] Our case presenting with a mutation of *CHD7* is also consistent with common findings in CHARGE syndrome with the *CHD7* mutation by Lalani et al[4] (cardiovascular malformations, coloboma, and facial palsy asymmetry).

Approximately 60–65% of CHARGE syndrome patients[4–6] have presented with the *CHD7* mutation since Vissers et al[7] found the genetic etiology in 2004. Variable phenotypes of CHARGE syndrome with the *CHD7* mutation have been confirmed by animal models. Anomalies of the vascular system were an expected phenotype from the *CHD7* mutation mouse model; however, no human cases have been reported.[8] Only one case of CHARGE syndrome has presented with a skull base vascular anomaly without the *CHD7* mutation.[10] *CHD7* molecular confirmation in our patient supports the vascular anomalies observed in animal models. CHARGE syndrome with a mutation in the SNF2 domain of *CHD7* has variable cardiovascular malformations.[4] However, our case presented with a frameshift mutation in the BRK domain, not the SNF2 domain.

Congenital absence of the ICA is a rare vascular anomaly, and only approximately 100 cases have been reported in the literature.[11] Agenesis of the ICA arises before 24 days of embryogenesis (3-mm fetal stage), when the ICA is developing from the terminal segments of the dorsal aorta and the third aortic arch arteries.[11,12] The definitive common carotid artery and most of the definitive branches of the external carotid artery are present by 40 days of embryogenesis (16–18-mm fetal stage).[11] The carotid channel develops in association with the ICA. The skull base does not begin to form until 5–6 weeks of fetal life. If the embryonic primordium of the ICA fails to develop early in embryonic life (before 3–5 embryonic weeks), the ICA and the carotid channel cannot develop.[11–13] Absence of both the ICA and the carotid channel in our patient is consistent with an insult having occurred before 3–5 weeks of fetal life and is compatible with previous pathogenesis that abnormal events of CHARGE syndrome occur at the end of the first month of development.[5]

Most of the reported patients with agenesis of the ICA were asymptomatic and were detected as an incidental finding because of developed collateral circulation.[13] Common symptoms and signs include recurrent headaches, blurring vision, hearing loss, hemiparesis with or without cranial nerve palsy, and intracranial hemorrhage due to ruptured aneurysms.[11–13] Other rare reported pathologic abnormalities associated with ICA agenesis are corpus callosum agenesis, neurofibromatosis, meningocele, coarctation of the aorta, and cardiac anomalies.[12] Even though we did not see any visible transcranial anastomosis, recurrent episodes of photophobia with vomiting were observed in our case. Since the child cannot develop adaptive skills in language because of severe hearing impairment, it is difficult to make a definite diagnosis of migraine. A possible explanation is migraine-like attacks, because the patient developed repetitive clinical symptoms of photophobia, vomiting and decreased activity, which responded well to cyproheptadine. In addition, the symptoms were similar to those of common clinical manifestation of agenesis of the ICA described previously.

In conclusion, we report a case of unilateral agenesis of the left ICA in a patient with CHARGE syndrome with a novel *CHD7* mutation. To the best of our knowledge, this is the first case of a vascular anomaly reported in a CHARGE syndrome patient with a confirmed *CHD7* mutation. The molecular mutation is located in the BRK domain, which is not the most common domain contributing to cardiovascular malformation in CHARGE syndrome. Interestingly, we also found that recurrent migraine-like attacks were relieved with cyproheptadine. We report this interesting association of unilateral agenesis of the ICA with CHARGE syndrome with the molecular defect delineated.

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